PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Febrile Illness Evaluation in a Broad Range of Endemicities (FIEBRE): Protocol for a multi-site prospective observational study of the causes of fever in Africa and Asia
AUTHORS	Hopkins, Heidi; Bassat, Quique; Chandler, Clare Isobel Rosina; Crump, John; Feasey, Nicholas A; Ferrand, Rashida; Kranzer, Katharina; Lalloo, David G; Mayxay, Mayfong; Newton, Paul N; Mabey, David

VERSION 1 – REVIEW

REVIEWER	Carsten Krüger University of Applied Sciences, Department of Applied Health Sciences, Bochum, Germany
REVIEW RETURNED	25-Jan-2020

GENERAL COMMENTS	I would like to thank the authors and the editor to get the opportunity to review this manuscript on such an important study protocol. I only have a few comments, please see my specific comments them below. Title and authorship The title represents the content of the article well. Key words: no specific comment Abstract The abstract summarises the manuscript very well. No specific comment Strengths and limitations of the study No specific comment Introduction This section gives a good overview of the background and the research question which is addressed in this study. One minor spelling mistake: page 6, line 33: bacterial pathogens Methods and Analysis Study design This section is well written and presents the methods and analysis plan appropriately, with a few minor exceptions. Page 7, line 19: write four instead of five!

	Page 7, lines 45-47: after “other diagnostic tests” insert a remark that these will be mentioned later in tables etc. Page 7, line 53: here already I was curious how the community controls would be selected. It did not become very clear to me after having read the entire manuscript (see below). Study sites, population and participant selection Page 8, line 21/22: same comment as above Data and sample collection at the time of patient enrolment (day 0) Page 9, lines 29-31: urine collection in young children is notoriously difficult. How can the authors ensure that they get a clean urine sample without contamination??? Please explain this. Otherwise many urine sample results will be prone to contamination, hence results would be unreliable. Data and sample collection at the time of patient follow-up (day 28) Page 9, line 57: how will the authors collect data on patients who are lost to follow-up or have died (perhaps even in community at home, not in a health facilty)??? Please explain. Data and sample collection for control participants Please clarify in this section where the controls are recruited: in the outpatient department? At home? This is not clear to me. Then how can the authors justify blood collection in these controls? What is the benefit for them? Please explain. Health care utilisation survey for estimation of incidence of infections No comment Qualitative research methods No comment Specific laboratory assessments No comment Sample archive No comment Data sharing No comment Sample size considerations No comment Data analysis plan for primary outcomes No comment Ethics and dissemination No comment Patient and public involvement No comment Discussion This is quite short, but discusses the expected outcome and implications well enough. Competing interests/Author contributions/Funding and Acknowledgements No comments. References No comments. Text box No comment

	Tables Table 1: no comment. Table 2a: line 25: fungaemia? The urine testing seems a little bit simple, no microscopy possible? Table 2b: No comment Table 2c: line 41: viraemia?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Carsten Krüger
Institution and Country
University of Applied Sciences, Department of Applied Health Sciences, Bochum, Germany
Please state any competing interests or state 'None declared':
None declared
Please leave your comments for the authors below
I would like to thank the authors and the editor to get the opportunity to review this manuscript on such an important study protocol. I only have a few comments, please see my specific comments them below.

Title and authorship
The title represents the content of the article well.
Key words: no specific comment
Abstract
The abstract summarises the manuscript very well. No specific comment

Strengths and limitations of the study
No specific comment

Introduction
This section gives a good overview of the background and the research question which is addressed in this study. One minor spelling mistake: page 6, line 33: bacterial pathogens

We would like to thank the reviewer for these kind comments on the overall value of the study protocol and the early sections of this manuscript. We have corrected the spelling mistake indicated, to "bacterial pathogens" (Introduction, page 5, line 18).

Methods and Analysis
Study design
This section is well written and presents the methods and analysis plan appropriately, with a few

minor exceptions.
Page 7, line 19: write four instead of five!

We thank the reviewer for catching this error in the original manuscript. All references to the number of study sites (including this one, now page 6, line 9) now correctly say “five” instead of “four”, due to the addition of a fifth study site in the time since our original manuscript submission, as described in our final comments at the end of this response letter.

Page 7, lines 45-47: after “other diagnostic tests” insert a remark that these will be mentioned later in tables etc.

This remark has been added (page 6, lines 25-26).

Page 7, line 53: here already I was curious how the community controls would be selected. It did not become very clear to me after having read the entire manuscript (see below).

Study sites, population and participant selection
Page 8, line 21/22: same comment as above

We thank the reviewer for identifying this gap, and have addressed these comments in the subsection on “Data sample collection for control participants”, as detailed below.

Data and sample collection at the time of patient enrolment (day 0)
Page 9, lines 29-31: urine collection in young children is notoriously difficult. How can the authors ensure that they get a clean urine sample without contamination??? Please explain this. Otherwise many urine sample results will be prone to contamination, hence results would be unreliable.

Getting urine samples, much less clean-catch samples, from young children is indeed difficult! We have added a parenthetical note to this effect (page 8, lines 18-19): “…a urine sample is collected from patients aged <2 years (using clean-catch methods where possible, although this is recognized to be challenging), and from…” We anticipate needing to describe the methods used, and the

implications for urine dipstick and microbiology results of contaminated (or unobtained) samples, in greater detail in future manuscripts reporting study results.

Data and sample collection at the time of patient follow-up (day 28)
Page 9, line 57: how will the authors collect data on patients who are lost to follow-up or have died (perhaps even in community at home, not in a health facilty)??? Please explain.

This is a good question; we have added information to answer it briefly as follows (page 9, lines 3-5): "In the event that a patient is lost to follow-up or deceased, information is collected from other household members where possible."

Data and sample collection for control participants
Please clarify in this section where the controls are recruited: in the outpatient department? At home? This is not clear to me. Then how can the authors justify blood collection in these controls? What is the benefit for them? Please explain.

As above, we thank the reviewer for identifying this gap, and agree that this should be clarified in the manuscript. We have added the following brief explanation (page 9, lines 15-16 and 18-21): "Potential control participants are approached at their place of residence by study staff, with assistance from established community health workers where locally appropriate. Controls are recruited twice monthly at each site and enrolled if they, or their parents/guardians, provide informed consent. The informed consent document and process for controls includes an explanation that control participants are not likely to benefit directly from study participation, but that their participation may lead to better understanding of febrile illnesses in their community and others like it."

Health care utilisation survey for estimation of incidence of infections
No comment
Qualitative research methods
No comment
Specific laboratory assessments
No comment
Sample archive
No comment
Data sharing

No comment
Sample size considerations
No comment
Data analysis plan for primary outcomes
No comment
Ethics and dissemination
No comment
Patient and public involvement
No comment

Discussion
This is quite short, but discusses the expected outcome and implications well enough.

Competing interests/Author contributions/Funding and Acknowledgements
No comments.

References
No comments.

Text box
No comment

Tables
Table 1: no comment.
Table 2a: line 25: fungaemia? The urine testing seems a little bit simple, no microscopy possible?

We have changed the spelling of “fungemia” to “fungaemia” as suggested; we are happy to use whichever spelling is preferred by *BMJ Open* editorial staff. Performing urine microscopy at the study sites would add substantially to the workload for study lab staff, and our estimation is that urine dipstick (for leucocyte esterase and nitrites, as described) gives adequate information to guide decisions on whether or not to perform culture urine. We have not changed the manuscript text or table to address this further.

Table 2b: No comment
Table 2c: line 41: viraemia?

We have changed the spelling of “viremia” to “viraemia” as suggested; we are happy to use whichever spelling is preferred by *BMJ Open* editorial staff.